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SCIENTIFIC COMMENTARY

Ready for human spinal cord repair?

We are in an exciting time where, based on successfully established animal models, a partial repair of the damaged human CNS appears to be feasible. A paper in the present issue of *Brain* (Mackay-Sim *et al.*, 2008) deals with the outcome after transplantation of olfactory ensheathing cells (OEC) in subjects with chronic spinal cord injury. An earlier report described the surgical and safety procedures in this trial (Feron *et al.*, 2005).

Presently, rehabilitation of spinal cord injury is limited to exploiting neuronal plasticity by functional training (Dietz, 2002). The combination of functional training and regenerative therapies, even if only limited structural repair is achieved, would certainly make an improved impact on outcome. There is an impressive number of promising approaches for inducing regeneration or limiting neuronal damage by neuroprotective treatments based on rodent experiments (for review see Raineteau and Schwab, 2001; Deumens *et al.*, 2005; Ramer *et al.*, 2005; Dietz and Curt, 2006). One is the application of regeneration-facilitating OEC at the lesion site. Convincing evidence was found that this approach leads to some spinal cord repair in rodent spinal cord injury (Li *et al.*, 1997; Ramon-Cueto *et al.*, 2000; Barnett and Chang, 2004).

The present article (Mackay-Sim *et al.*, 2008) reports on the effect of this approach in six chronic complete (ASIA A) spinal cord injury subjects (phase I/IIa design) with regular follow-up using clinical, electrophysiological (MEP), imaging (MRI) and functional (Functional Independence Measure, FIM) examinations over 3 years. Thus, the present study, in contrast to other OEC trials (Huang *et al.*, 2003; Lima *et al.*, 2006), was carefully designed on the basis of standards established during the past few years (Steeves *et al.*, 2007). Such a study design is in line with the consensus that clinical examinations alone are insufficient reliably to monitor any therapeutic effect of a new interventional therapy (Curt *et al.*, 2004). Additional neurophysiological and functional examinations allow for some differentiation between compensation, neuronal plasticity and regeneration as principal factors underlying an improvement of function after a spinal cord injury (Curt *et al.*, 2008). Meanwhile, the Spinal Cord Independence Measure (SCIM) has been established for functional testing in spinal cord injury subjects (Catz *et al.*, 2001).

The results described by Mackay *et al.* (2008) must be considered preliminary because of the small number of spinal cord injury subjects included. In addition, the therapeutic effect of cell transplantation on outcome was not the primary goal of this study, although a comparison was made with a control group of spinal cord injury subjects. Overall, there were no adverse findings 3 years after autologous OEC transplantation. Only one spinal cord injury subject showed some sensory gain, but no functional recovery; in all other treated subjects no change in clinical and functional tests was detected. Also, the imaging and electrophysiological examinations remained unchanged over the course of the study. For this category of a complete spinal cord injury (ASIA A) such an outcome corresponds to the natural history (Curt *et al.*, 2008). The results appear disappointing in view of the promising animal experiments. How can this be explained? During the last 10 years we have become increasingly aware of the problems associated with such translational studies, due to the complexity of this field (Dietz and Curt, 2006). There are several interpretations that might be offered.

First, the adequacy of the animal spinal cord injury model on which the clinical study is based has to be considered. There are some animal models that fit poorly with the human condition. For example, the frequently used transection model (cf. Raineteau and Schwab, 2001; Bennett *et al.*, 2004; Klapka *et al.*, 2005) does not reflect the human condition, where the contusional lesion usually extends over several segments of the spinal cord. However, a contusion rat model shows similar electrophysiological and imaging results as well as outcome in function as human spinal cord injury (Metz *et al.*, 2000). Similarly, the spastic movement disorder after spinal cord injury never shows a motoneuronal hyperactivity (Dietz and Sinkjaer, 2007) as described for the rat with a sacral spinal cord injury (Bennett *et al.*, 2004).

Second, thoracic lesions are usually studied in animal models (Gensel *et al.*, 2006), whereas injury to the cervical cord is most common in humans (Curt *et al.*, 2008). Also, in the trial discussed here (Mackay-Sim *et al.*, 2008), spinal cord injury subjects with thoracic lesions were included in order to minimize the risk of any additional loss of function as a result of this procedure, with the consequence of recruitment difficulties. In the cervical lesion, every segment gained would have a great impact on function, whereas in subjects with thoracic damage, improvement of locomotor function can only be achieved if regenerating fibres make contact with the long propriospinal neurons (Raineteau and Schwab, 2001). However, cervical and thoracolumbar spinal cord injuries are always associated with damage to the peripheral nervous system (up to 40% of paresis might be due to a damage of motoneurons and roots; Collazos-Castro *et al.*, 2005). This deficit would possibly not be affected by an intervention directed at spinal tract regeneration.

Third, new interventional therapies are frequently applied in chronic spinal cord injury subjects aiming to achieve clinical stability (Mackay-Sim *et al.*, 2008). However, recent studies in chronic spinal cord injury describe demyelination around the injury cavities (Guest *et al.*, 2005), scar formation (Klapka *et al.*, 2005) and degradation of spinal neuronal function below the level of the lesion (Dietz and Muller, 2004). Thus, even if regeneration of tract fibres is achieved through intervention, this may not necessarily be matched by functional improvement. Therefore, for most current studies, early intervention is recommended (cf. Dietz and Curt, 2006).

Fourth, no functional training was performed in the present trial (Mackay-Sim *et al.*, 2008). In contrast to humans, rodents train themselves automatically after spinal cord injury. There is evidence that functional training does facilitate appropriate re-connections by regenerating fibre tracts after spinal cord injury (Edgerton *et al.*, 1997; de Leon *et al.*, 1999; Dietz and Harkema, 2004).

Fifth, a number of mechanisms after spinal cord injury prevent a spontaneous regeneration of fibre tracts (e.g. scar formation and expression of Nogo protein and chondroitin sulphate). This has prompted corresponding approaches to overcome these hurdles and to induce/facilitate regeneration of damaged fibres (for review see Raineteau and Schwab, 2001; Ramer *et al.*, 2005; Dietz and Curt, 2006). Therefore, as exemplified in the rat, the use of complementary approaches involving Schwann cell bridges, OEC and chondroitinase might be applied to human subjects in the future in order to enhance the number of regenerating fibres and improve the prospects of functional recovery (Fouad *et al.*, 2005).

The last point concerns problems, which are well discussed in the paper of Mackay-Sim *et al.* (2008), of achieving an optimal versus an ethically acceptable design including the issue of whether or how to include sham-surgical controls. With the availability of a detailed description of the natural history of spinal cord injury in a great number of subjects (Curt *et al.*, 2008), the control group in a trial can be kept relatively small.

Based on the above points we can learn important lessons from the work of Mackay-Sim *et al.* (2008) and hope to make such trials more successful in the future.

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Volker Dietz
Spinal Cord Injury Centre, Balgrist University Hospital,
Forchstr. 340
8008 Zürich,
Switzerland
E-mail: volker.dietz@balgrist.ch

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